(19) JAPANESE PATENT OFFICE (JP)

(12) Official Gazette for Laid-Open Patent Applications (A)

(11) Japanese Laid-Open Patent Application (Kokai) No. 8-20597

(51) Int.Cl.8	Ident. Symbols	Internal Office Nos. FI
C07K 6/06		8318-4H
C07D 277/28		
277/56		
471/12		

(43) Laying-Open Date: 23 January 1996

Request for Examination: Not yet requested

Number of Claims: 3 OL (Total of 13 pages)

(21) Application No.: 6-156006

(22) Application Date: 7 July 1994

(71) Applicant: 000006091
Meiji Pharmaceutical Company, Ltd.
4-16 Kyobashi 2-chome, Chuo-ku
Tokyo-to

(72) Inventor: Tsuneo Okonogi
c/o General Drug Product Research Laboratories
Meiji Pharmaceutical Company, Ltd.
760 Morooka-cho, Kohoku-ku
Yokohama-shi, Kanagawa-ken

(72) Inventor: Seiji Tsutsumi
c/o General Drug Product Research Laboratories
Meiji Pharmaceutical Company, Ltd.
760 Morooka-cho, Kohoku-ku
Yokohama-shi, Kanagawa-ken

(72) Inventor: Yoshio Akiyama
c/o General Drug Product Research Laboratories
Meiji Pharmaceutical Company, Ltd.
760 Morooka-cho, Kohoku-ku
Yokohama-shi, Kanagawa-ken

continued on last page

[continuation on page 13]

(72) Inventor: Shokichi Ouchi
c/o General Drug Product Research Laboratories
Meiji Pharmaceutical Company, Ltd.
760 Morooka-cho, Kohoku-ku
Yokohama-shi, Kanagawa-ken

(72) Inventor: Emiko Hatsushiba
c/o General Drug Product Research Laboratories
Meiji Pharmaceutical Company, Ltd.
760 Morooka-cho, Kohoku-ku
Yokohama-shi, Kanagawa-ken

[return to page 1]

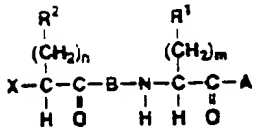
(54) [Title of the Invention] Heterocyclic Carbonyl Compounds a Thrombin Inhibiting Action

(57) [Abstract]

[Objective]

[Structure] This invention relates to compounds and pharmacologically permissible salts thereof as indicated by general formula (I) below that have inhibitory activity against thrombin and that can be used in preventing and treating thrombosis.

[Chemical Formula 18]



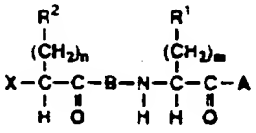
(I)

[Wherein, A indicates a heterocyclic group, R^1 indicates an alkyl group, a guanidino group, an amidino group, an amidinothio group, an amino group, an hydroxyl group, a mercapto group, a lower alkoxy group or a phenyl group that may be substituted, B indicates an amino acid residue, R^2 indicates a methyl group, a cycloalkyl group, an aryl group, a heteroaryl group or an arylthio group, X indicates a hydrogen atom, an hydroxyl group, an amino group, a halogen atom, an alkylamino group, an acylamino group or an alkoxycarbonylamino group, m indicates an integer of 1 to 50 and n indicates an integer of 0 to 4.]

[Claims]

[Claim 1] Heterocylic compounds and pharmacologically permissible salts thereof as indicated by general formula (I) below.

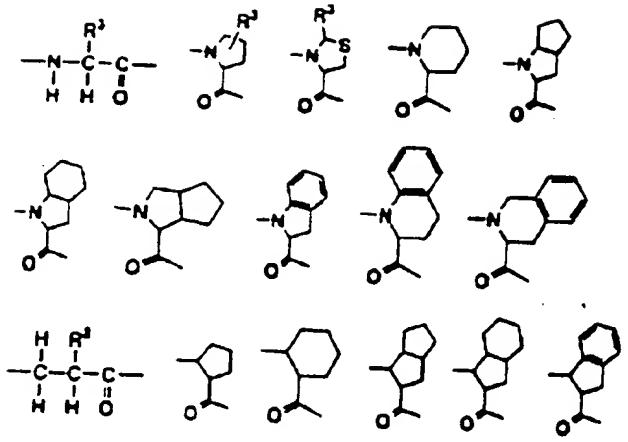
[Chemical formula 1]



(I)

[Wherein, A indicates a monoheterocyclic ring which is a 5 member or 6 member saturated, partially saturated or unsaturated ring having at least 1 nitrogen atom or diheterocyclic ring in which benzene rings or pyridine rings are condensed (which heterocyclic rings may have oxygen atoms, iodine atoms or three or less separate nitrogen atoms, in which monoheterocyclic rings, the carbon atoms in the ring, and, in which diheterocylcic rings, the carbon atoms in the benzene ring or the pyridine ring, may be substituted by lower alkyl groups having 1 to 4 carbons atoms, halogens, hydroxyl groups, amino groups or mercaptan groups, and which rings may be bonded to the carbonyl group by any of the carbon atoms that form the heterocyclic rings), R^1 indicates an alkyl group having 1 to 4 carbon atoms and which may be branched, a guanidino group, an amidinothio group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a lower alkoxy group or a phenyl group that may be substituted by a guanidino group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a halogen, B indicates a residue that will be selected from the following substances

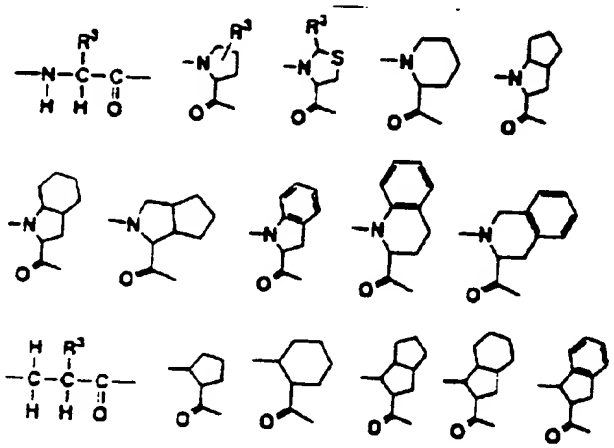
[Chemical Formula 2]



(wherein, R^1 is an alkyl group having 1 to 6 carbon atoms and which may be branched, a phenyl group or a phenylmethyl group), R^2 indicates a methyl group, an aryl group, a cycloalkyl group, a heteroaryl group, a arylthio group or a methyl group that is bonded with X, X indicates a hydrogen atom, an hydroxyl group, an amino group, a halogen atom, an alkylamino group having 1 to 4 carbon atoms, an acylamino group, an alkoxycarbonylamino group or an aryloxycarbonylamino group, m indicates an integer of 1 to 5 and n indicates an integer of 0 to 4).

[Claim 2] A heterocyclic carbonyl compound in which, in general formula (I) in Claim 1, A indicates a thiazole, an oxazole, an imidazole, a thiazoline, an oxazoline, an imidazoline, a pyridine, a pyrimidine, a pyrazole, a 1,2,4-thiadiazole, a 1,2,4-oxadiazole, a 1,2,4-triazole (which heterocyclic rings are bonded to the carbonyl group by any of the carbon atoms of which they are formed), a benzothiazole, a benzooxazole, a benzoimidazole, a thiazolo[5,4-b]pyridine, a thiazolo[4,5-b]pyridine or an imidazo[4,5-b]pyridine (which heterocyclic rings are bonded to the carbonyl group by the carbon atom in the 2nd position), R^1 indicates a guanidino group, an amidinothio group, an amidino group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a lower alkoxy group or a phenyl group that may be substituted by a guanidino group, an amidino group, an amino group, an hydroxyl group, a mercapto group or halogens, B indicates a residue that is selected from substances of the following formulas

[Chemical Formula 3]



(wherein R^1 has the same significances as defined in general formula (I)), R indicates a methyl group, a phenyl group that may have substituted groups, a thienyl group, a pyridyl group, an indolyl group, a naphthyl group, a diphenylmethyl group, a cyclopentyl group, a cyclohexyl group, a phenylthio group or methylene that is bonded with X, X indicates a hydrogen atom, an hydroxyl group, an amino group, a halogen atom, an alkylamino group with 1 to 4 carbon atoms, an acylamino group, an alkoxycarbonylamino group or an aryloxycarbonylamino group, m indicates an integer of 1 to 5 and n indicates an integer of 0 to 4.

[Claim 3] A thrombin inhibitor that contains the heterocyclic compounds described in Claims 1 or 2 or pharmacologically permissible salts thereof as its effective components.

[0001]

[Field of industrial use] This invention relates to novel heterocyclic carbonyl compounds that have thrombin inhibiting action.

[0002]

[Prior art] Known compounds that exhibit thrombin inhibiting activity are described, for example, in Japanese Patent Application Early Disclosure No. 54-100342 [1979] and U.S. Patents No. 4399065 and 4927809. However, these existing compounds do not have sufficient thrombin inhibiting activity. Therefore, there is a demand for compounds having higher activity and enzyme selectivity.

[Synopsis of the invention]

[0003]

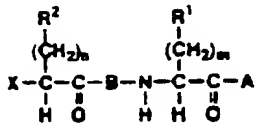
[Problems the invention is intended to solve] On the basis of research on protease inhibitors, the inventors discovered a group of novel compounds that have thrombin inhibiting activity. Consequently, this invention has the objective of providing novel heterocyclic carbonyl compounds having thrombin inhibiting activity. This invention has the further objective of providing thrombin inhibitors that contain these novel heterocyclic carbonyl compounds having thrombin inhibiting action as their effective components.

[0004]

[Means for solving the problems] The heterocyclic carbonyl compounds of this invention are the compounds indicated by general formula 1 below and pharmacologically permissible salts thereof.

[0005]

[Chemical Formula 4]

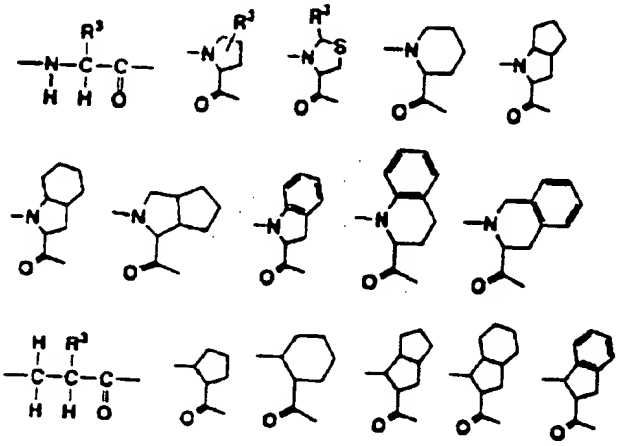


(I)

[Wherein, A indicates a monoheterocyclic ring which is a 5 member or 6 member saturated, partially saturated or unsaturated ring having at least 1 nitrogen atom or diheterocyclic ring in which benzene rings or pyridine rings are condensed (which heterocyclic rings may have oxygen atoms, sulfur atoms or three or less separate nitrogen atoms, in which monoheterocyclic rings, the carbon atoms in the ring, and, in which diheterocyclic rings, the carbon atoms in the benzene ring or the pyridine ring, may be substituted by lower alkyl groups having 1 to 4 carbons atoms, halogens, hydroxyl groups, amino groups or mercaptan groups, and which rings may be bonded to the carbonyl group by any

of the carbon atoms that form the heterocyclic rings), R^1 indicates an alkyl group having 1 to 4 carbon atoms and which may be branched, a guanidino group, an amidinothio group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a lower alkoxy group or a phenyl group that may be substituted by a guanidino group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a halogen, B indicates a residue that can be selected from the following substances

[Chemical Formula 5]



[wherein R^1 has the same significances as defined in general formula (I)), R indicates a methyl group, a phenyl group that may have substituted groups, a thienyl group, a pyridyl group, an indolyl group, a naphthyl group, a diphenylmethyl group, a cyclopentyl group, a cyclohexyl group, a phenylthio group or methylene that is bonded with X, X indicates a hydrogen atom, an hydroxyl group, an amino group, a halogen atom, an alkylamino group with 1 to 4 carbon atoms, an acylamino group, an alkoxycarbonylamino group or an aryloxycarbonylamino group, m indicates an integer of 1 to 5 and n indicates an integer of 0 to 4.

Further, the thrombin inhibitor and anticoagulant of this invention are substances that contain the compounds of the aforementioned general formula (I) and pharmacologically permissible salts thereof. The compounds of the aforementioned general formula (I) of this invention have strong thrombin inhibiting activity and are useful as medicinal drugs.

[0007] [Specific description of the invention] The substituted group indicated by A in general formula (I) is a monoheterocyclic ring which is a 5 member or 6 member saturated, partially saturated or unsaturated ring having at least 1 nitrogen atom or diheterocyclic ring in which benzene rings or pyridine rings are condensed (which heterocyclic rings may have oxygen atoms, iodine atoms or three or less separate nitrogen atoms, in which monoheterocyclic rings, the carbon atoms in the ring, and, in which diheterocylcic rings, the carbon atoms in the benzene ring or the pyridine ring, may be substituted by lower alkyl groups having 1 to 4 carbons atoms, halogens, hydroxyl groups, amino groups or mercaptan groups, and which rings may be bonded to the carbonyl group by any of the carbon atoms that form the heterocyclic rings). Preferably, they are monoheterocyclic rings such as a thiazole, an oxazole, an imidazole, a thiazoline, an oxazoline, an imidazoline, a pyridine, a pyrimidine, a pyrazole, a 1,2,4-thiadiazole, a 1,2,4-oxadiazole or a 1,2,4-triazole ring (which heterocyclic rings are bonded to the carbonyl group by any of the carbon atoms of which they are formed) or a diheterocylcic ring such as a benzothiazole, a benzooxazole, a benzoimidazole, a thiazolo[5,4-b]pyridine, a thiazolo[4,5-b]pyridine or an imidazo[4,5-b]pyridine ring (which heterocyclic rings are bonded to the carbonyl group by the carbon atom in the 2nd position).

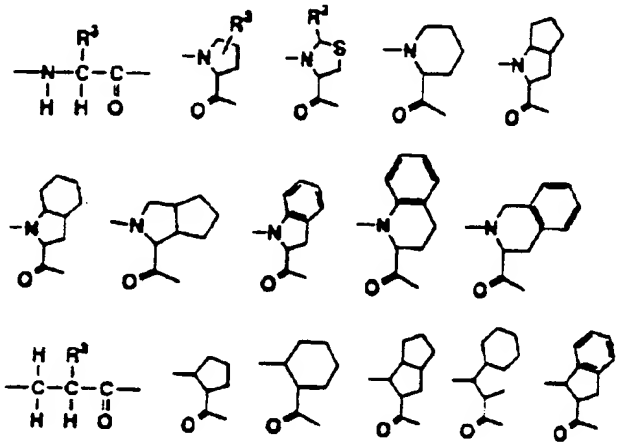
[0008] In addition, the substituted group indicated by R1 in general formula (I) is a methyl group, an isopropyl group, a guanidino group, an amidinothio group, an amidino group, an amino group, a hydroxyl group, a mercapto group, a lower alkoxy group or a phenyl group that may be substituted by a guadinino [sic] group, an amidino group, an amino group, a hydroxyl group, a mercapto group or a halogen atom and m is an integer of 1 to 5.

Preferably, R1 is a guanidino group, an amidino group or an amino group or a phenyl group that is substituted by a guanidino group, an amidino group or an amino group and m is an integer of 3 to 5.

[0009] The residues indicated by B in general formula (I) are α-amino acids, amino acid residues or straight chain or cyclic carbonyl compounds. Preferably, they are residues selected from compounds of the following structural formulas.

[0010]

[Chemical Formula 6]



(Wherein, R^3 has the same significances as defined in general formula (I).)

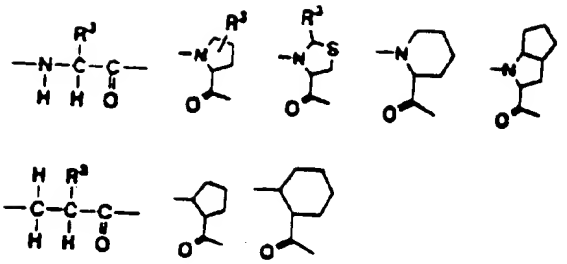
[0011] The substituted group indicated by R^2 in general formula (I) is an alkyl group that may be branched, an aryl group, a phenyl group that may be substituted, a cycloalkyl group, a heterocyclic saturated (aromatic) ring that contains 1 or 2 nitrogen atoms or a 5- or 6-member heterocyclic saturated (aromatic) ring that contains one oxygen atom or sulfur atoms, in which methylene is bonded with A and in which n is an integer of 0 to 5. Preferably, R^2 is a phenyl group, a diphenylmethyl group, a biphenyl group, a naphthyl group, a pyridyl group, a pyrrole group, an indolyl group, a thienyl group, a furanyl group or a phenylthio group and the heterocyclic ring that is formed by the methylene that is bonded with X is pyrrolidine or piperidine and n is an integer of 0 to 2.

[0012] The substituted groups indicated by X in general formula (I) are hydrogen, halogens, hydroxyl groups, amino groups, alkylamino groups, acylamino groups and alkoxycarbonylamino groups. Preferably, they are amino groups, methylamino groups, acetylamino groups, phenylacetylamino groups, benzyloxycarbonylamino groups and t-butoxycarbonylamino groups.

[0013] The desirable compound groups of this invention are compounds in which, in general formula (I), A is a thiazole, R^1 is a guanidino group, B is a residue selected from substances of the following structural formulas

[0014]

[Chemical Formula 7]

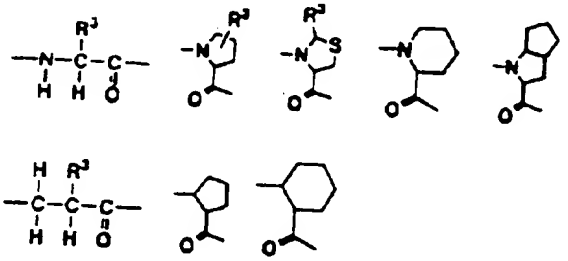


(wherein R^3 has the same significance as defined for general formula (I)), R is an aryl group, a cycloalkyl group or a phenylthio group, X is hydrogen, an amino group or a benzyloxycarbonylamino group, m is 3 and n is 0 or 1 and compounds in which A is a thiazole, R^1 is an amino group, B is a residue selected from substances of the following structural formulas

[0015]

7

[Chemical Formula 8]



(wherein R^3 has the same significance as defined for general formula (I)), R is an aryl group, a cycloalkyl group or a phenylthio group, X is hydrogen, an amino group or a benzyloxycarbonylamino group, m is 4 or 5 and n is 0 or 1.

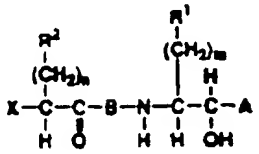
[0016] Desirable specific compounds of this invention include, for example, D-phenylalanyl-N-[1-[2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-pyrroline amide,
D-cyclohexylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-pyrroline amide,
D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-octahydroindole-2-carboxyamide,
D-phenylglycyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide,
(benzyloxycarbonyl)-D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide,
acetyl-D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide,
phenylpropionyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide, 2-[N-[2-(phenylthioacetyl)cyclopenta-1-ylcarbonyl]-L-alginyl]thiazole,
D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-5-aminopentyl]-L-proline amide and
D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-6-aminohexyl]-L-proline amide.

[0017] Stereoisomers attributable to the carbon atoms in the molecule can be present in the compounds of this invention. All stereoisomers are included in this invention. The compounds of this invention can be salts. These salts are salts that are pharmacologically permissible. Preferably, they can be salts of hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid, acetic acid, citric acid, maleic acid, succinic acid, lactic acid, tartaric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid.

[0018] The compounds of general formula (I) can be synthesized by various methods. For example, compounds of general formula [IV]

[0021]*

[Chemical Formula 11]

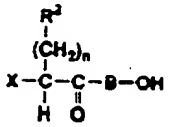


(IV)

(wherein, R^1, R^2, A, B, X, m and n have the same significances as defined previously) can be obtained by reacting compounds as indicated by general formula (II) below

[0019]

[Chemical Formula 9]

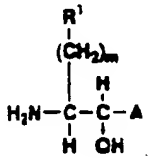


(II)

(wherein, R^2, X, B and n have the same significances as defined in general formula (I) and X indicates a group having a protective group) and compounds as indicated by general formula (III) below

[0020]

[Chemical Formula 10]



(wherein, R^1, A and m have the same significances as defined in general formula (I) and R^1 indicates a group having a protective group) with a suitable coupling reagent. When protective groups are necessary for R^1 and X in the synthesis, protective groups that are used in peptide chemistry can generally be used. Preferably, they can be t-butoxycarbonyl groups, benzyloxycarbonyl groups and 4-methoxy-2,3,6-trimethylbenzenesulfonyl groups.

[0022] Reagents that are used in peptide chemistry can be used as the coupling reagents. Desirable coupling reagents include, for example, N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, N,N'-bis[2-oxo-3-oxazolidinyl]phosphonediamide acid chloride and diphenylphosphinyl chloride. In the presence of these reagents, the reaction can be performed in a suitable solvent (for example, ethyl acetate, acetonitrile, methylene chloride, DMF) at -70 to 30°C, and, preferably, -30 to 10°C.

---

*Translator's note: To provide proper English syntax, the sections have been rearranged from the Japanese.

[0023] Next, the hydroxyl group of compound (IV) is oxidized to form a ketone. As required, the protective group can be removed and the heterocyclic carbonyl compound of general formula (I) can be obtained. The oxidation reaction can be performed with dimethyl sulfoxide using various types of additives as described in Synthesis, 1990, page 857. Oxidation can also be performed by means of tetra-n-propylammonium perthenate [phonetic]**, pyridinium dichromate and pyridinium chlorochromate. Oxidation by means of dimethyl sulfoxide in the presence of oxalyl chloride is preferable. For example, the compounds of general formula (I) can be obtained by reacting a reagent prepared from oxalyl chloride and dimethyl sulfoxide with compound (IV) at -70 to 0°C using methylene chloride as the solvent, after which treatment is performed with triethylamine.

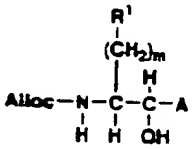
[0024] Moderate reaction conditions can be selected to obtain compounds of general formula (I) when a reaction to eliminate protection is required. For example, when the protective groups described above are used, the protection can be eliminated by hydrocracking using palladium-carbon as the catalyst or by an acid decomposition reaction in which trifluoroacetic acid is reacted in the presence of anisole and thioanisole.

[0025] The compounds of general formula (I) of this invention form acid addition salts with various inorganic acids and organic acids. Compound (I) that is obtained by the aforementioned reactions can be isolated in free form or in the form of a salt. When it is in free form, the acid addition salt can be obtained by reaction with the desired acid.

[0026]* In order to obtain the aforementioned amine compound (III), which is the starting substance, the carbinol compound (VII)

[0029]

[Chemical Formula 14]

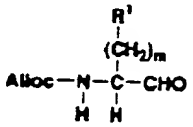


(VII)

can be obtained by reacting the aminocarbinol compound (V), which is obtained by the method described in Chemical Review, 1989, Vol. 89, page 149,

[0027]

[Chemical Formula 12]



(V)

wherein R' and m have the same significances as defined in general formula (II) and Alloc indicates allyloxycarbonyl group) with the silyl compound (VIIa) described in Journal of Heterocyclic Chemistry, 1971, Vol. 8, page 257 and Journal of Organic Chemistry, 1988, Vol. 53, page 1748.

**Translator's note: Transliterated phonetically from the Japanese. As such, the spelling may differ from other transliterations.

[0028]

[Chemical Formula 13]

$(CH_3)_3Si\text{-}A$ (VIa)

(wherein A has the same significances as defined in general formula (I)). Preferably, this reaction can be performed using methylene chloride as the solvent at 0 to 50°C in the presence or absence of cerium fluoride and tetrabutylammonium fluoride. Compound (VII) can also be obtained by treating the heterocyclic compound (H-A), which is the starting substance, with a base such as n-butyl lithium in an inactive solvent (for example, tetrahydrofuran and dimethoxyethane) to form compound (VIb)

[0030]

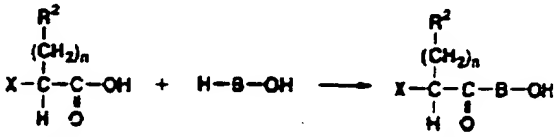
[Chemical Formula 15]

Li^+A^- (VIb)

which is then reacted with the aforementioned compound (V). The aforementioned amine compound (III) can be obtained by treating and eliminating the amino group protective group of compound (VII), for example, pyrrolidine in the presence of $Pd(Ph_3P)_4$, which is a known method. The aforementioned carboxylic acid compound (II), which is also a starting substance, can be obtained by ordinary methods of peptide chemistry when B-OH is an amino acid residue. Compound (II) can be obtained by introducing the carboxylic acid compound (VIII) into a reactive derivative (for example, an acid halide, an acid anhydride or an active ester) and by reacting it with an alkali metal salt of the amino acid (IX) or a salt of an organic base. Preferably, compound (VIII) can be reacted with N-hydroxysuccinic acid amide to convert it to an active ester which is then reacted with the amino acid (IX) in the presence of an organic base to form a peptide bond.

[0032]

[Chemical Formula 16]

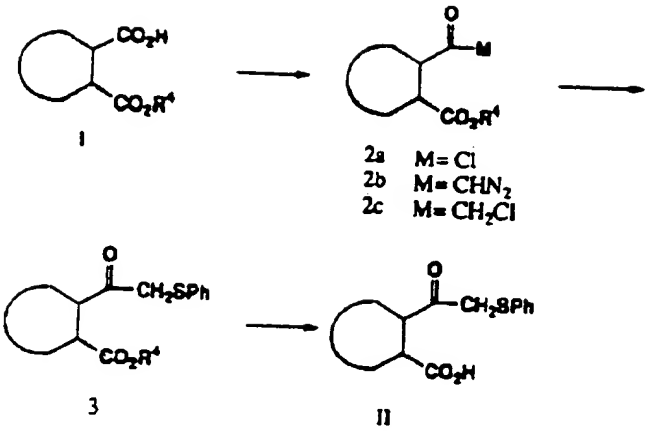


(VIII) (IX) (II)

When B-OH of the aforementioned compound (II) is an aliphatic carboxylic acid, it can be obtained from a cyclic or straight chain dicarboxylic acid. For example, with a cyclic dicarboxylic acid, the monoalkyl ester (1) is reacted with a thionyl chloride or oxalyl chloride to form an acid chloride (2a), which is then treated with diazomethane to convert it to diazomethyl ketone (2b). This ketone is reacted with anhydrous hydrogen chloride to form the chloromethyl ketone (2c), which is then converted to phenylthiomethyl ketone (3) by treating it with thiophenyl. The carboxylic acid compound (II) can be obtained by hydrolyzing the ester of this compound.

[0033]

[Chemical Formula 17]



(Wherein, R^4 indicates a methyl group, a benzyl group or a diphenylmethyl group.)

[0034] Because compound (I) of this invention and its acid addition salts exhibit a strong, selective inhibitory action against thrombin, it is useful as a diagnostic drug for determining thrombin in the blood, as a platelet coagulation inhibitor and in the prevention and treatment of thrombosis.

[0035] Thrombin inhibitors which contain compounds of this invention as indicated by general formula (I) and pharmacologically permissible salts thereof as their effective components can be used in various forms suited to oral and parenteral administration (for example, inhalation administration, nose drops, eye drops, subcutaneous administration, intravenous injection, intramuscular injection, etc.)

[0036] For example, depending on its intended use, they can be prepared as oral agents in such forms as tablets, capsules, granules, powders, fine grains, troches, syrups and emulsions, as inhalation agents, as solutions for topical use in the form of nose drops and eye drops and as injection agents for intravenous injection and intramuscular injection. These preparations can be manufactured by standard methods using vehicles, extending agents, binders, wetting agents, disintegrators, lubricants, dispersants, buffering agents, preservatives, auxiliary dissolution agents, antiseptics and stabilizers that are commonly used.

[0037] The content of the compound of this invention in a drug preparation differs depending on the form of the preparation. Ordinarily, it is 1 to 70 wt%, and, preferably, 5 to 50 wt %, of the total composition. The dose and the method of administration are determined appropriately taking into consideration the age and sex of the patient and the degree of symptoms. Ordinarily, for adults, it should be on the order of approximately 0.1 to 2000 mg, and, preferably, 5 to 400 mg, per day. It can be administered once or several times a day.

[0038] Method of determination of in vitro inhibitory activity

Thrombin inhibiting activity in an in vitro system was found by the method described in the European Journal of Biochemistry, 1988, Vol. 172, page 17. A mixed solution of 100 ml of 0.1 M trishydrochloric acid solution (pH 8.0; containing 0.3 M NaCl and 2 mM $CaCl_2$), a 10 ml DMSO solution of the compound of this invention, 50 ml of bovine serum albumin solution (0.4 mg/ml) and 20 ml of thrombin (0.5 U/ml) dissolved in the aforementioned trishydrochloric

acid solution was prepared. To this was added 20 ml of 5 mM Boc-Asp(OBzl)-Pro-Arg-methylcoumarin amide solution (10% DMSO), which was the substrate and the mixture was incubated for 30 minutes at 37°C, after which fluorescence intensity (a1) of 440 nm excited by 380 nm UV was determined. At the same time, an experiment was performed in which DMSO was used instead of the solution of the compound of this invention and fluorescence intensity (a2) was determined in the same way. In addition, the fluorescence intensity (b) of a mixed solution of 120 ml of the aforementioned 0.1 M trishydrochloric acid buffer solution, 10 ml of DMSO solution, 50 ml of bovine serum albumin solution and 20 ml of substrate solution was determined as background. Inhibition rates were calculated by the following formula and the concentration required for 50% inhibition (IC_{50}) was found.

$$\text{Inhibition rate (\%)} = [[(a2-b) - (a1-b)] / (a2-b)] \times 100$$

The experimental results for representative compounds of this invention are shown in Table 1.

Table 1. Thrombin Inhibition Activity

Example No. of compound	50% inhibition concentration
1	0.0015
2	0.16
4	0.012
5	0.32
7	0.007
8	0.002
Argatroban*	0.065

* Compound described in Japanese Patent Disclosure No. 61-46829 (1986)

[0039]

[Examples] We shall now describe the compounds of this invention in detail by presenting examples as indicated below. However, they are simply illustrations and do not limit this invention in any way.

[0040] Example 1

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

(a)
t-butoxycarbonyl-D-phenylalanyl-N-[1-[(2-thiazolyl)hydroxymethyl]-4-[N',N"-bis(t-butoxycarbonyl)aminoiminomethyl]amino]butyl]-L-proline amide

t-butoxycarbonyl-D-phenylalamyl-L-proline (300 mg, 0.82 mmol), 2-[2-amino-5-[N',N"-bis(t-butoxycarbonyl)aminoiminomethyl]amino-1-hydroxypentyl]thiazole (367 mg, 0.82 mmol) and N-hydroxbenzotriazole (110 mg, 0.82 mmol) were dissolved in 15 ml of acetonitrile and 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (187 mg, 0.98 mmol) was added as the materials were being ice-cooled. The mixture was stirred at the same temperature for 3 hours. The temperature was then raised to room temperature and it was stirred for 15 hours. The reaction mixture was concentrated, after which it was dissolved in ethyl acetate, washed with water and dried in $MgSO_4$. The solvent was removed, the crude product was purified by flash chromatography and the target compound (497 mg, 77%) was obtained.

^{1}H-NMR($CDCl_3$) δ 1.42-1.62 (m, 32H), 1.79-1.89 (m, 2H), 2.47-2.50 (m, 1H), 1.93-3.00 (m, 2H), 3.33-3.43 (m, 4H), 4.01-4.04 (m, 1H), 4.26-4.29 (m, 1H), 4.43-4.60 (m, 1H), 4.98-5.02 (m, 1H), 5.47-5.50 (m, 1H), 7.15-7.29 (m, 6H), 7.71-7.75 (m, 1H), 8.33-8.36 (m, 1H).

[0041] (b)
D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-proline amide

Oxazolyl chloride (79 ml, 0.91 mmol) was dissolved in 8 ml of methylene chloride, dimethyl sulfoxide (129 ml, 0.91 mmol) was added at -40°C and the mixture was stirred for 5 minutes. 5 ml of methylene chloride solution containing the aforementioned compound (480 mg, 0.61 mmol) was added and the mixture was stirred for 30 minutes at -40 to -30°C. Next, triethylamine (581 ml, 4.1 mmol) was added and the mixture was stirred at the same temperature for 30 minutes, after which it was emptied into ice water. The organic layer was separated and washed with water, after which it was desiccated with $MgSO_4$ and concentrated. The product was refined by flash chromatography and t-butoxycarbonyl-D-phenylalanyl-N-[1-[(2-thiazolyl) carbonyl]-4-[N',N"-bis(t-butoxycarbonyl)aminoiminomethyl]amino]butyl]-L-proline amide (407 mg, 86%) was obtained. This compound was dissolved in 1 ml of anisole and 4 ml of trifluoroacetic acid was added as the materials were being ice cooled. The mixture was stirred at the same temperature for 30 minutes and was then stirred at room temperature for 30 minutes. The reaction mixture was concentrated, dissolved in 5 ml of water and washed with ether, after which it was freeze dried and the target substance (407 mg) was obtained. ^{1}H-NMR(D_2O) δ 1.59-1.60 (m, 32H), 1.70-1.91 (m, 2H), 2.12-2.14 (m, 2H), 2.75-2.81 (m, 1H), 3.15-3.29 (m, 4H), 3.50-3.54 (m, 1H), 4.43-4.46 (m, 1H), 4.53-4.61 (m, 1H), 5.49-5.55 (m, 1H), 7.32-7.46 (m, 5H), 8.11-8.15 (m, 2H), MS (SIMS) m/z (M^{+1}).

[0042] (c) Synthesis of intermediate

The 2-[2-amino-5-[N',N"-bis(t-butoxycarbonyl)aminoiminomethyl]amino-1-hydroxypentyl]thiazole that was used in this example was synthesized by the following method. L-arginine (10 g, 57 mmol) was dissolved in 60 ml of water, allyl chloroformate (8.99 mg, 74 mmol) was added under ice-cooled conditions as the pH was maintained at 9 to 10 with 4N-NaOH, the pH was adjusted to 7 and the mixture was stirred at the same temperature for 2 hours. The precipitate that separated out was collected by filtration and was washed with a small quantity of ice water and acetone. It was then desiccated and N-allyloxycarbonyl-L-arginine (13.3 g, 90%) was obtained. The aforementioned compound (10 g, 39 mmol) and p-toluenesulfonic acid (7 g, 37 mmol) was dissolved in 250 ml of methanol, diphenyldiazomethane (15 g, 78 mmol) was added over a one hour period and the mixture was stirred for 3 hours at room temperature, after which it was concentrated. The reaction product was dissolved in chloroform and washed with water, after which it was desiccated with $MgSO_4$ and concentrated, with N-allyloxycarbonyl-L-arginine diphenylmethyl ester p-toluenesulfonate (24 g) being obtained. The aforementioned crude product (24 g) was dissolved in 250 ml of acetonitrile, dimethylaminopyridine (4.7 g, 39 mmol) and bis-t-butyldicarbonate (21 g, 97 mmol) were added and the mixture was stirred for 15 hours at room temperature, after which it was concentrated. The reaction mixture was dissolved in ethyl acetate and washed in water, after which it was concentrated. It was then refined by silica gel chromatography (n-hexane/ethyl acetate) and Nα-allyloxycarbonyl-N',N"-bis(t-butoxycarbonyl)-L-arginine diphenyl methyl ester (14.5 g, 60%) was obtained.

[0043] The aforementioned compound (11 g, 18 mmol) was dissolved in 150 ml of tetrahydrofuran. $LiBH_4$ (0.75 g, 35 mmol) was added and the mixture was stirred for 2 hours at room temperature. The reaction mixture was poured into acidic water at pH 3, extraction was performed with ethyl acetate and the organic layer was washed with water, after which it was desiccated with $MgSO_4$ and concentrated. The reaction product was refined by silica gel chromatography (n-hexane/ethyl acetate) and Nα-allyloxycarbonyl-N',N"-bis(t-butoxycarbonyl)- L-arginol (3.9 g, 50%) was obtained.

^{1}H-NMR($CDCl_3$) δ 1.35-1.80 (m, 22H), 3.30-3.80 (m, 6H), 4.58 (d, J = 5.02 Hz, 1H), 5.22 (dd, J = 1.55, 10.0 Hz, 1H), 5.31 (dd, J = 1.55, 17.6 Hz, 1H), 5.49 (d, J = 7.53 Hz, 1H), 5.93 (ddd, J = 5.02, 10.0, 17.6 Hz, 1H), 8.38

(t, J = 5.02 Hz, 1H). Oxazolyl chloride (1.27 g, 10 mmol) was dissolved in 40 ml of methylene chloride, dimethyl sulfoxide (1.57 g, 20 mmol) was added at -30°C, after 5 minutes, 20 ml of methylene chloride solution containing the aforementioned carbinol compounds (3.0 g, 6.7 mmol) was added and the mixture was stirred for 30 minutes at -30°C. Next, triethylamine (4.62 g, 45 mmol) was added and the mixture was stirred for 30 minutes at -30°C, after which it was emptied into ice water and the solutions were separated. The organic layer was washed with water, after which it was desiccated with $MgSO_4$ and concentrated, with
Nα-allyloxycarhbonyl-N',N"-bis(t-butoxycarbonyl)-L-arginal (2.9 g) being obtained.

[0044] The aforementioned crude product (2.9 g) and 2-trimethylsilylthiazole (1.54 mg, 9.8 mmol) were dissolved in 50 ml of methylene chloride and the solution was stirred for 5 hours at room temperature. 1M tetra-n-butylammonium fluoride THF solution (10.4 ml) was added, the mixture was stirred for another 30 minutes and was then emptied into ice water. The organic layer was separated, desiccated with $MgSO_4$ and concentrated. It was then refined by silica gel chromatography (n-hexane/ethyl acetate) and 2-[2-allyloxycarbonylamino-5-[N',N"-bis(t-butoxycarbonyl)aminoiminomethyl]amino-1-hydroxypentyl]thiazole (2.1 g, 60%) was obtained.

^{1}H-NMR($CDCl_3$) δ 1.35-1.86 (m, 22H), 3.30-3.55 (m, 2H), 4.05-4.22 (m, 1H), 4.43-4.65 (m, 2H), 5.06-5.40 (m, 4H), 5.78-6.02 (m, 2H), 7.28 (d, J = 3.0 Hz, 1H), 7.73 (d, J = 3.0 Hz, 1H), 8.48 (t, J = 6.24 Hz, 1H).

[0045] The aforementioned compound (2.1 g) was dissolved in 35 ml of methylene chloride, piperidine (1.34 g, 19 mmol) and $Pd(Ph_3P)_4$ (220 mg, 0.19 mmol) was added and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was concentrated and refined by silica gel chromatography (chloroform/methanol), with the target compound (1.42 g, 85%) being obtained.

^{1}H-NMR($CDCl_3$) δ 1.40-1.80 (m, 22H), 3.17-3.55 (m, [sic] 4.70-4.80 (m, 1H), 4.88-4.98 (m, 1H), 7.40-7.80 (m, 3H), 8.30-8.43 (m, 1H).

[0046] Example 2

2-[2-[2-(phenylthioacetyl)cyclopenta-1-ylcarbonyl]-L-arginyl]thiazole

(a)
2-[2-[2-(phenylthioacetyl)cyclopenta-1-ylcarbonyl]amino-5-[N',N'-bis(t-butixycarbonyl)aminoiminomethyl]amino-1-hydroxypentyl]thiazole

2-(phenylthioacetyl)cyclopentanecarboxylic acid (249 mg, 0.94 mmol), 2-[2-amino-5-[N',N'-bis(t-butoxycarbonyl)aminoiminomethyl]amino-1-hydroxypentyl]thiazole (417 mg, 0.94 mmol) and N-hydroxybenzotriazole (126 mg, 0.94 mmol) were dissolved in 20 ml of acetonitrile,
1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (215 mg, 0.98 mmol) was added under ice-cooled conditions, the mixture was stirred at this same temperature for 3 hours, the temperature was then raised to room temperature and it was stirred for 15 hours. The reaction mixture was concentrated, after which it was dissolved in ethyl acetate. It was then washed with water, after which it was desiccated with $MgSO_4$. The solvent was removed, the crude product was refined by flash chromatography and the target compound (438 mg, 68%) was obtained.

^{1}H-NMR($CDCl_3$) δ 1.20-2.10 (m, 28H), 2.87 (m, 1H) 3.30-3.50 (m, 3H), 3.24 (m, 1H), 4.25 (m, 1H), 5.03 (m, 1H), 6.75 (m, 1H), 7.15-7.40 (m, 5H), 7.43-7.57 (m, 1H), 7.70 (m, 1H), 8.37 (m, 1H).

[0047] (b) 2-[2-(phenylthioacetyl)cyclopentane-1ylcarbonyl-L-arginyl]thiazole
oxalyl chloride (81 ml, 0.93 mmol) was dissolved in 10 ml of methylene chloride, dimethyl sulfoxide (132 ml, 1.87 mmol) was added at -40°C and the mixture was stirred for 5 minutes. 5 ml of methylene chloride solution containing the aforementioned compound (430 mg, 0.62 mmol) was added and the mixture was stirred for 30 minutes at -40 to -30°C. Next, triethylamine (596 ml, 4.2 mmol) was added and the mixture was stirred at this same

temperature for 30 minutes, after which it was emptied into ice water. The organic layer was separated and washed with water, after which it was desiccated with $MgSO_4$ and concentrated. The product was purified by flash chromatography and
2-[2-(phenylthioacetyl)cyclopentane-1-ylcarbonyl-N',N'-bis(t-butoxycarbonyl) arginyl]thiazole (350 mg, 83%) was obtained. This compound was dissolved in 1 ml of anisole, 4 ml of trifluoroacetic acid was added under ice-cooled conditions, the mixture was stirred at this same temperature for 30 minutes and was then stirred for 30 minutes at room temperature. The reaction mixture was concentrated and refined by flash chromatography (chloroform/methanol), with the target compound (254 mg) being obtained.

^{1}H-NMR(CD_3OD) δ 1.60-2.20 (m, 10H), 3.05 (m, 1H) 3.24 (m, 2H), 3.53 (m, 1H), 3.90 (m, 2H), 5.56 (m, 1H), 7.10-7.40 (m, 1H), 7.10-7.40 (m, 5H), 8.05 (m, 1H), 8.12 (m, 1H), MS(FD) m/z 488 (M^+).

[0048] (c) Synthesis of intermediate

The 2-phenylthiomethylcarbonylcyclopentane-1-carboxylic acid that was used in this example was synthesized by the following method.
2-[(diphenyl) methoxycarbonyl]cyclohexane-1-carboxylic acid (2.0 g, 6.17 mmol) and triethylamine (0.944 ml, 6.79 mmol) were dissolved in 20 ml of methylene chloride, N,N-dimethylformamide (1 drop) and oxalyl chloride (855 mg, 6.79 mmol) were added under ice-cooled conditions and the mixture was stirred for 1 hour. Next, an ether solution containing an excess of diazomethane was added under ice-cooled conditions and the mixture was stirred for 30 minutes. A 4N-HCl dioxane solution (2.31 ml) was then added and the mixture was stirred for another 30 minutes. The reaction product was concentrated, the chloromethyl ketone that was produced was dissolved in 30 ml of tetrahydrofuran, disiopropyl ethylamine (815 mg, 6.32 mmol) and thiophenol (690 mg, 6.32 mmol) were added and the mixture was stirred for 3 hours at room temperature, after which it was concentrated. The reaction product was refined by silica gel chromatography (toluene/acetic acid) and phenylthiomethyl ketone (2.12 g, 86%) was obtained. This product was dissolved in 200 ml of methanol, a 1M aqueous solution of potassium carbonate (9.74 ml) was added and the mixture was stirred for 15 hours at room temperature. The reaction mixture was concentrated and the residue was dissolved in water and washed with ether. The aqueous layer was acidified, after which extraction was performed with ethyl acetate. It was then desiccated with $MgSO_4$ and concentrated, with the target compound (0.97 g, 76%) being obtained.

^{1}H-NMR($CDCl_3$) δ 1.60-2.10 (m, 6H), 3.20 (m, 1H) 3.58 (m, 1H), 3.80 (s, 2H), 7.15-7.40 (m, 5H).

[0049] Example 3

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-5-aminopentyl]-L-proline amide

(a) t-butoxycarbonyl-D-phenylalanyl-N-[1-[2-thiazolyl)hyxroxymethyl]-5-(benzyloxycarbonylamino)pentyl]-L-proline amide, t-butoxycarbonyl-D-phenylalanyl-L-proline (255 mg, 0.70 mmol), 2-[2-amino-6-(benzyloxycarbonyl) amino-1-hydroxybenzotriazole (94mg, 0.70 mmol) and N-hydroxybenaotriazole (94 mg, 0.70 mmol) were dissolved in 15 ml of acetonitrile, 1-ethyl-3- (3'-dimethylaminopropyl)carbodiimide hydrochloride (160 mg, 0.84 mmol) was added under ice-cooled conditions, the mixture was stirred at this same temperature for 3 hours, the temperature was raised to room temperature and the mixture was then stirred for 15 hours. The reaction mixture was concentrated, after which it was dissolved in ethyl acetate. It was then washed with water, after which it was desiccated with $MgSO_4$. The solvent was removed, the crude product was refined by flash chromatography (ethyl acetate) and the target compound (393 mg, 81%) was obtained.

^{1}H-NMR($CDCl_3$) δ 1.20-2.15 (m, 20H), 2.40-2.80 (m, 1H), 2.90-3.47 (m, 3H) 3.65-3.77 (m, 1H), 4.23-4.58 (m, 3H), 4.95-5.04 (m, 2H), 5.04-5.30 (m, 2H), 5.30-5.56 (m, 2H) 7.04-7.90 (m, 12H).

[0050] (b) D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-5-aminopentyl]-L-proline amide

Oxalyl chloride (72 ml, 0.84 mmol) was dissolved in 3 ml of methylene chloride, dimethyl sulfoxide (119 ml, 1.68 mmol) was added at -40°C and the mixture was stirred for 5 minutes. 5 ml of methylene chloride solution containing the aforementioned compound (390 mg, 0.56 mmol) was added and the mixture was stirred for 30 minutes at -40 to -30°C. Next, triethylamine (394 ml, 2.81 mmol) was added and the mixture was stirred for 30 minutes at this same temperature, after which it was emptied into ice water. The organic layer was separated and washed with water, after which it was desiccated with $MgSO_4$ and concentrated. The product was refined by flash chromatography (hexane/ethyl acetate) and t-butoxycarbonyl-D-phenylalanyl-N-[1-[(2-thiazolyl) carbonyl]-5-(benzyloxycarbonyl)aminopentyl]-L-proline amide (388 mg, 73%) was obtained. This compound was dissolved in formic acid (3.5 ml), Pd (150 mg) was added and the mixture was stirred for 3 hours at room temperature. The reaction mixture was filtered, after which the filtrate was concentrated, the product was dissolved in 1 ml of anisole, trifluoroacetic acid (3 ml) was added under ice-cooled conditions and the mixture was stirred at this same temperature for 30 minutes. The reaction mixture was concentrated and was dissolved in 5 ml of water. It was then washed with water, after which freeze-drying was performed and the target substance (190 mg) was obtained.

^{1}H-NMR(D_2O) δ 1.25-2.04 (m, 7H), 2.04-2.18 (m, 1H), 2.64-2.82 (m, 2H), 3.00-3.70 (m, 6H), 4.30-4.45 (m, 2H), 5.45-5.55 (dd, J = 4.14, 9.31 Hz, 1H), 7.20-7.55 (m, 5H), 7.70-8.20 (m, 2H); MS(FD) m/z 458 (M^+).

[0051] (c) Synthesis of intermediate

The 2-[2-amino-6-(benzyloxycarbonyl)amino-1-hydroxyhexyl]thiazole that was used in this example was synthesized by the same method as in Example 1c using Nα-allyloxycarbonyl-Nω-bensyloxycarbonyl-L-lysine methyl ester as the starting substance.

^{1}H-NMR($CDCl_3$) δ 1.20-1.80 (m, 6H), 1.80-1.96 (m, 1H), 3.10-3.34 (m, 3H) 3.60-3.80 (m, 1H), 4.70 (d, J = 3.78 Hz, 1H), 4.80-4.97 (m, 1H), 5.01 (s, 2H), 7.29 (d, J = 2.52 Hz, 1H), 7.30-7.38 (m, 5H) 7.73 (d, J = 2.52 Hz, 1H).

[0052] Example 4

D-cyclohexylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized by the same method as in Example 1 from t-butoxycarbonyl-D-cyclohexylalanyl-L-proline and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 1.00-1.55 (m, 4H), 1.55-2.25 (m, 14H), 2.30-2.40 (m, 1H), 3.22-3.30 (m, 2H), 3.58-3.70 (m, 1H), 3.72-3.82 (m, 1H), 4.39 (dd, J = 3.45, 13.8 Hz, 1H), 4.56 (dd, J=8.6 Hz, 1H), 4.80-5.80 (m, 1H), 8.10-8.23 (m, 2H), MS(SIMS) m/z 492 (M^{+1}).

[00053] Example 5

D-phenylglycyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized by the same method as in Example 1 from t-butoxycarbonyl-D-phenylglycyl-L-proline and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 1.62-1.97 (m, 8H), 2.10-2.20 (m, 1H), 2.98-3.06 (m, 1H), 3.22-3.30 (m, 1H), 3.63-3.72 (m, 1H), 4.58 (dd, J = 3.40, 8.60 Hz, 1H), 5.38-5.43 (m, 1H), 5.50-5.60 (m, 1H), 7.45-7.60 (m, 5H), 8.10 (d, 1H), 8.20 (d, 1H); MS(SIMS) m/z 472 (M^{+1}).

[0054] Example 6

D-tyrosyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized by the same method as in Example 1 from t-butoxycarbonyl-D-tyrosyl-L-proline and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 1.75-2.04 (m, 6H), 2.16-2.36 (m, 2H), 3.04-3.10 (m, 1H), 3.25-3.28 (m, 6H), 3.45-3.46 (m, 1H), 3.70-3.76 (m, 1H) 4.52-4.77 (m, 2H), 5.52-5.56 (m, 1H), 6.85-6.96 (m, 2H), 7.19-7.26 (m, 2H), 8.13-8.19 (m, 2H), MS(SIMS) m/z 504 (M^{+1}).

[0055] Example 7

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-octahydroindole-2-carboxyamide

It was synthesized by the same method as in Example 1 from t-butoxycarbonyl-D-phenylalanyl-L-octahydroindole-2-carboxylic acid and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 0.87-1.05 (m, 2H), 1.10-1.23 (m, 3H), 1.36-1.49 (m, 3H), 1.58-1.82 (m, 5H), 1.91-2.03 (m, 2H), 2.85-3.00 (m, 2H), 3.15-3.20 (m, 3H), 4.20-4.25 (m, 1H), 4.34 (dd, J = 5.4, 10.3 Hz, 1H), 5.38 (dd, J = 4.0, 8.4 Hz, 1H), 7.19-7.36 (m, 5H), 7.98-8.04; MS(SIMS) m/z 540 (M^{+1}).

[0056] Example 8

Benzyloxycarbonyl-D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized in the same way as in Example 1 from benzyloxycarbonyl-D-phenylalanyl-L-proline and the compound of Example 1c.

^{1}H-NMR($CDCl_3$) δ 1.40-2.20 (m, 7H), 2.59-2.80 (m, 1H), 2.90-3.50 (m, 5H), 3.50-3.80 (m, 1H) 4.28-4.54 (m, 1H), 4.54-470 (m, 1H), 5.04 (ABq, J = 13.8, 39.7 Hz, 1H), 5.45-5.70 (m, 1H), 6.18-6.30 (m, 1H), 6.90-7.50 (m, 10H), 7.65 (d, J = 7.36 Hz, 1H), 7.84 (d, J = 7.36 Hz, 1H), 7.94-8.04 (m, 1H); MS SIMS m/z 620 (M^{+1}).

[0057] Example 9

Acetyl-D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized in the same way as in Example 1 from acetyl-D-phenylalanyl-L-proline and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 1.50-2.50 (m, 11H), 2.52-2.75 (m, 2H), 2.97-3.13 (m, 2H), 3.15-3.50 (m, 2H), 3.65-3.80 (m, 1H), 4.35-4.50 (m, 1H), 5.35-5.50 (m, 1H), 7.23-7.56 (m, 5H), 8.00-8.22 (m, 2H), MS(SIMS) m/z 528 (M^{+1}).

[0058] Example 10

3-phenylpropionyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized by the same method as in Example 1 from 3-phenylpropionyl- L-proline and the compound of Example 1c

^{1}H-NMR(D_2O) δ 1.50-2.50 (m, 6H), 2.50-3.25 (m, 8H), 3.25-3.57 (m, 2H), 4.28-4.38 (m, 1H), 5.40-5.46 (m, 1H), 7.20-7.40 (m, 5H), 7.60-7.70 (m, 1H), 8.00-8.10 (m, 1H); MS(SIMS) m/z 471 (M^{+1}).

[0059] Example 11

4-phenylbutanoyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized in the same way as in Example 1 from 4-phenylbutanoyl-L- proline and the compound of Example 1c.

^{1}H-NMR($CDCl_3$) δ 1.72-1.75 (m, 2H), 1.89-2.09 (m, 5H), 2.26-2.51 (m, 5H), 2.61-2.68 (m, 2H), 3.13-3.56 (m, 4H) 4.42-4.53 (m, 1H), 5.59 (brs, 1H), 7.08-7.28 (m, 5H), 7.70 (d, J = 3.1 Hz, 1H), 7.77-7.90 (m, 2H), 8.00 (d, J = 3.1 Hz, 1H), MS(SIMS) m/z = 485 (M^{+1}).

[0060] Example 12

D-propyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized in the same way as in Example 1 from t-butoxycarbonyl- D-pyrrolyl-L-proline and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 1.70-2.20 (m, 9H), 2.30-2.45 (m, 1H), 2.47-2.65 (m, 2H), 3.25-3.35 (m, 1H), 3.40-3.55 (m, 2H), 3.60-3.68 (m, 1H), 3.70-3.80 (m, 1H), 3.80-3.90 (m, 1H), 4.58 (dd, J = 3.40, 5.17 Hz, 1H), 4.68 (dd, J = 6.90, 7.59 Hz, 1H), 5.51 (dd, J = 5.17, 9.31 Hz, 1H), 8.12 (d, J = 3.40 Hz, 1H), 8.18 (d, J = 3.40 Hz, 1H); MS(FD) m/z 435 (M^+).

[0061] Example 13

2-[2-(phenylthioacetyl)cyclohexa-1-ylcarbonyl-L-arginyl]thiazole

It was synthesized in the same method as in Example 2 from 2-(phenylthioacetyl)cyclohexanecarboxylic acid and the compound from Example 1c.

^{1}H-NMR(CD_3OD) δ 1.10-2.20 (m, 12H), 2.63 (m, 1H), 3.02 (m, 1H), 3.09-3.23 (m, 2H), 3.83-4.09 (m, 2H), 5.47-5.55 (m, 1H), 7.05-7.40 (m, 5H), 8.02 (m, 1H), 8.10 (m, 1H); MS(SIMS) m/z 502 (M^{+1}).

[0062] Example 14

4-phenylbutanoyl-N-[1-[(2-thiazolyl)carbonyl]-5-aminopentyl]-L-proline amide

It was synthesized in the same method as in Example 3 from 4-phenylbutanoyl-L-proline and the compound of Example 3c.

^{1}H-NMR(D_2O) δ 1.40-2.25 (m, 10H), 2.35 (m, 2H), 2.65 (m, 2H), 2.99 (m, 2H), 3.42-3.52 (m, 4H), 4.40 (m, 1H), 5.46 (m, 1H), 7.10-7.40 (m, 5H), 8.05 (m, 1H), 8.11 (m, 1H); MS(SIMS) m/z 457 (M^{+1}).

[0063] Example 15

3-phenylpropionyl-N-[1-[(2-thiazolyl)carbonyl]-5-aminopentyl]-L-proline amide

It was synthesized in the same method as in Example 3 from 3-phenylpropionyl-L-proline and the compound of Example 3c.

^{1}H-NMR(D_2O) δ 1.20-1.90 (m, 7H), 1.90-2.20 (m, 2H), 2.50-3.00 (m, 5H), 3.20-3.54 (m, 2H), 4.29-4.37 (m, 1H), 5.39 (dd, J = 3.75, 8.00 Hz, 1H), 7.12-7.35 (m, 5H), 7.98 (d, J = 2.77 Hz, 1H), 8.06 (d, J = 2.77 Hz, 1H): MS(SIMS) m/z 443 (M^{+1}).

[0064] Example 16

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-6-aminohexyl]-L-proline amide

It was synthesized in the same method as in Example 3 from t-butoxycarbonyl-D-phenylalanyl-L-proline and 2-[2-amino-7-(benzyloxycarbonyl) amino-1-hydroxypentyl]thiazole.

^{1}H-NMR(D_2O) δ 1.20-1.90 (m, 9H), 2.00-2.20 (m, 2H), 2.74 (ddd, J = 6.90, 7.24, 7.59 Hz, 1H), 2.98-3.10 (m, 2H), 3.10-3.32 (m, 2H), 3.39-3.50 (m, 1H), 4.44 (dd, J = 4.83, 9.66 Hz, 1H), 4.50-4.60 (m, 1H), 5.48 (dd, J = 4.14, 9.66 Hz, 1H), 7.25-7.50 (m, 5H), 8.10 (d, J = 2.41 Hz, 1H), 8.15 (d, J = 2.41 Hz, 1H): MS(SIMS) m/z 471 (M^{+1}).

[0065] Example 17

3-phenylpropionyl-N-[1-[(2-thiazolyl)carbonyl]-6-aminohexyl]-L-proline amide

It was synthesized in the same method as in Example 3 from 3-phenylpropionyl-L-proline and 2-[2-amino-7-(benzyloxycarbonyl) amino-1-hydroxyheptyl]thiazole

^{1}H-NMR(D_2O) δ 1.20-1.90 (m, 10H), 1.90-2.08 (m, 1H), 2.08-2.30 (m, 1H), 2.54-2.85 (m, 1H), 2.85-3.06 (m, 6H), 3.25-3.35 (m, 1H), 3.40-3.61 (m, 2H), 4.41 (d, J = 6.90 Hz, 1H), 5.43 (dd, J = 3.45, 8.60 Hz, 1H), 7.14-7.37 (m, 5H), 8.02 (d, J = 24 Hz, 1H), 8.08 (d, J = 24 Hz, 1H): MS(FD) m/z 456 (M^{+}).

[0066] Example 18

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-methoxybutyl]-L-proline amide

It was synthesized in the same method as in Example 1 from t-butoxycarbonyl-D-phenylalanyl-L-proline and 2-2(-amino-1-hydroxy-5-methoxypentyl)thiazole.

^{1}H-NMR($CDCl_3$) δ 1.57-1.59 (m, 1H), 1.73-1.88 (m, 5H), 2.07-2.14 (m, 2H), 2.75-2.78 (m, 1H), 3.20-3.33 (m, 2H), 3.35 (s, 3H), 3.49-3.56 (m, 3H), 4.42 (dd, J = 4.2, 8.5 Hz, 1H), 4.53 (m, 1H), 5.49 (dd, J = 4.3, 8.4 Hz, 1H), 7.31-7.34 (m, 2H), 7.41-7.46 (m, 3H), 8.09 (d, J = 3.1 Hz, 1H), 8.14 (d, J = 3.1 Hz, 1H), MS(FD) m/z = 459 (M^{+1}).

[0067] Example 19

D-phenylalanyl-N-[1-[(2-benzothiazolyl)carbonyl]-4-methoxybutyl]-L-proline amide

It was synthesized in the same method as in Example 1 from t-butoxycarbonyl-D-phenylalanyl-L-proline and 2-2(-amino-1-hydroxy-5-methoxypentyl)benzothiazole.

^{1}H-NMR($CDCl_3$) δ 1.74-1.78 (m, 1H), 1.80-1.93 (m, 4H), 2.04-2.19 (m, 2H), 2.73-2.74 (m, 1H), 3.15-3.28 (m, 2H), 3.35 (s, 3H), 3.54-3.58 (m, 4H), 4.40-4.45 (m, 1H), 4.50-4.54 (m, 1H), 5.56 (dd, J = 4.3, 8.4 Hz, 1H), 7.24-7.43 (m, 5H), 7.67-7.73 (m, 2H), 8.15-8.26 (m, 2H); MS(SIMS) m/z = 509 (M^{+1}).

[0068] Example 20

t-butoxycarbonyl-D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-methoxybutyl]-L-proline amide

It was synthesized from t-butoxycarbonyl-D-phenylalanyl-L-proline and 2-(2-amino-1-hydroxy-5-methoxypentyl)thiazole and was obtained as the intermediate of Example 18.

^{1}H-NMR(D_2O) δ 1.51-1.90 (m, 14H), 2.15-2.23 (m, 2H), 2.62-2.66 (m, 1H), 3.01-3.04 (m, 2H), 3.30 (s, 3H), 3.38-3.44 (m, 3H), 3.54-3.57 (m, 1H), 4.49-4.62 (m, 2H), 5.40-5.43 (m, 1H), 5.75-5.79 (m, 1H), 7.18-7.32 (m, 5H), 7.53-7.61 (m, 2H), 7.95-7.98 (m, 1H), 8.18-8.21 (m, 1H); MS(FD) m/z 558 (M^+).

[0069] Example 21

t-butoxycarbonyl-D-phenylalanyl-N-[1-[(2-benzothiazolyl)carbonyl]-4-methoxybutyl]-L-proline amide

It was synthesized from t-butoxycarbonyl-D-phenylalanyl-L-proline and 2-(2-amino-1-hydroxy-5-methoxypentyl)benzothiazole and was obtained as the intermediate of Example 19.

^{1}H-NMR(D_2O) δ 1.43 (s, 9H), 1.51-1.67 (m, 4H), 1.80-1.89 (m, 2H), 2.07-2.21 (m, 2H), 2.61-2.63 (m, 1H), 2.90-3.05 (m, 2H), 3.30 (s, 3H), 3.33-3.40 (m, 2H), 3.51-3.54 (m, 1H), 4.44-4.68 (m, 1H), 4.62-4.64 (m, 1H), 5.44-5.47 (m, 1H), 5.55-5.62 (m, 1H), 7.20-7.31 (m, 5H), 7.63-7.65 (m, 1H), 7.68 (d, J = 3.0 Hz, 1H), 8.02 (d, J = 3.0 Hz, 1H); MS(FD) m/z 608 (M^+).

[0070] Example 22

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-2-phenylethyl]-L-proline amide

It was synthesized by the same method as in Example 1 from t-butoxycarbonyl-D- phenylalanyl-L-proline and 2-(2-amino-1-hydroxy-3-phenylpropyl)thiazole.

^{1}H-NMR($CDCl_3$) δ 1.49-1.54 (m, 2H), 1.60-1.80 (m, 1H), 2.10-2.14 (m, 1H), 2.59-2.67 (m, 1H), 2.85-2.97 (m, 2H), 3.10-3.19 (m, 1H), 3.28-3.49 (m, 2H), 3.64-3.75 (m, 1H), 4.50-4.54 (m, 1H), 5.88-5.93 (m, 1H), 7.20-7.36 (m, 10H), 7.67-7.78 (m, 2H), 8.06-8.08 (m, 1H); MS(SIMS) m/z = 477 (M^{+1}).

[0071] Example 23

4-phenylbutanoyl-N-[1-[(2-thiazolyl)carbonyl]ethyl]-L-proline amide

It was synthesized by the same method as in Example 1 from 4-phenylbutanoyl-L-proline and 2-(2-amino-1-hydroxypropyl)thiazole.

^{1}H-NMR($CDCl_3$) δ 1.52 (d, J = 6.90 Hz, 1H), 1.80-2.30 (m, 6H), 2.30-2.38 (m, 2H), 2.68-2.74 (m, 2H), 3.30-3.40 (m, 1H), 3.45-3.52 (m, 1H), 4.62 (dd, J = 2.41, 9.31 Hz, 1H), 5.69 (q, J = 6.90 Hz, 1H), 7.18-7.31 (m, 5H), 7.69 (d, J = 3.10 Hz, 1H), 8.02 (d, J = 3.10 Hz, 1H); MS(FD) m/z = 399 (M^+).

(19)日本国特許庁（ＪＰ）　(12) 公開特許公報（A）　(11)特許出願公開番号

特開平8－20597

(43)公開日　平成８年(1996)１月23日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ｃ０７Ｋ　5/06		8318－4H		
Ｃ０７Ｄ 277/28				
277/56				
471/12				

審査請求　未請求　請求項の数３　ＯＬ　（全 13 頁）

(21)出願番号　特願平6－156006

(22)出願日　平成６年(1994)７月７日

(71)出願人　000006091
明治製菓株式会社
東京都中央区京橋２丁目４番16号

(72)発明者　小此木　恒夫
神奈川県横浜市港北区師岡町760番地　明治製菓株式会社薬品総合研究所内

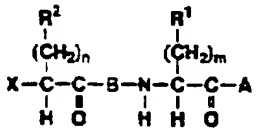
(72)発明者　堤　誠司
神奈川県横浜市港北区師岡町760番地　明治製菓株式会社薬品総合研究所内

(72)発明者　秋山　佳央
神奈川県横浜市港北区師岡町760番地　明治製菓株式会社薬品総合研究所内

最終頁に続く

(54)【発明の名称】　トロンビン阻害作用を有する複素環カルボニル化合物

(57)【要約】
【目的】
【構成】　本発明は、トロンビンに対し阻害活性を有し、血栓症の予防や治療に用いられる一般式（Ｉ）で表される化合物並びにその薬理学上許容される塩に関する。
【化１８】



(I)

[式中、Aは複素環式基、R[1]はアルキル基、グアニジノ基、アミジノ基、アミジノチオ基、アミノ基、水酸基、メルカプト基、低級アルコキシ基、置換されていてもよいフェニル基、Bはアミノ酸残基、R[2]はメチル基、シクロアルキル基、アリール基、ヘテロアリール基、アリールチオ基、Xは水素原子、水酸基、アミノ基、ハロゲン原子、アルキルアミノ基、アシルアミノ基、アルコキシカルボニルアミノ基、mは１～５の整